REMARKS

The First Two Rejections under 35 U.S.C. §103

The rejections of claims 1, 6-9 and 11-15 under 35 U.S.C. §103, as being obvious over Ambuhl (US Pub. No. 2004/0198645) in view of Hauel (AU-B-10707/92) or further in view of Gaviraghi (WO 00/27397) and Ohkouchi (US Pub. 2004/0180085), are respectfully traversed.

Applicants maintain their previous arguments in traversal of the rejections, the most pertinent points being re-phrased below. However, applicants first address the "Response to Arguments" section of the Office action. For the following reasons, applicants urge that the Response to Arguments does not refute applicants' position.

First, the grounds of rejection rely heavily on the allegation that Hauel teaches that the meglumine used only in Example II of the reference is used to solubilize telmisartan. However, neither Hauel – nor any other evidence of record – supports such a conclusion. Hauel provides no explanation at all why the meglumine is used. Hauel says the active is dissolved but does not say that the meglumine is effective for such dissolution. Further, Example II is not directed to any specific active. It is clearly a prophetic example related to an undefined active. One of ordinary skill in the art could not have any expectation of whether the meglumine could solubilize any specific active because the active is not specified in the example. One of ordinary skill in the art – from viewing Hauel -- could not have any reasonable expectation of what the meglumine does to the active when the active is not specified. Certainly, there is no expectation from this isolated and unexplained example of Hauel of what effect meglumine would have specifically on telmisartan. One of ordinary skill in the art would know that the ability of one compound to solubilize another is highly dependent on the specific combination and there is no teaching of a specific combination in Hauel's composition examples. For this reason alone, the grounds of rejection are not supported by the evidence. There is certainly no reasonable expectation from the cited prior art that meglumine would effectively solubilize telmisartan.

Second, the only teaching of meglumine in Hauel is the isolated Example II which relates to providing a liquid ampoule dose. There is no reasonable expectation from this teaching that meglumine would be useful for solubilizing (or some other use) in the tablet, powder or capsule compositions of Ambuhl. A component useful for providing a liquid

composition would not be expected to have the same usefulness in a solid composition. The ampoule composition of Example II of Hauel also uses glycofurol which is a solvent component used in compositions for intravenous or intramuscular injections. Further, the composition does not contain a water-soluble diluent. Such a formulation would not be considered by one of ordinary skill in the art to have any applicability for modifying a composition – such as of Ambuhl – which is specifically required to be in a solid tablet, powder or capsule form.

Third, there is a failure of the "articulated reasoning with some rational underpinning to support the legal conclusion of obviousness" required by KSR International Co. v. Teleflex Inc., 550 U.S. 398, 82 USPQ2d 1385, at 1396 (2007). Applicants fail to see any rational reason (other than hindsight reconstruction of the claimed compositions) to take one component out of an isolated example regarding liquid compositions in Hauel which relates to an unspecified active agent generically including telmisartan and combine this one component into the highly specified solid composition of Ambuhl which is specific to cyclosporin. The alleged motivation to combine is that both cyclosporin and telmisartan are "poorly water soluble" drugs. But the term "poorly water soluble" is a vague term. In the context in which Ambuhl uses this term, there is no reasonable suggestion to one of ordinary skill in the art that its teachings could be applied to every drug which may have some undefined extent of a water solubility issue. The only specific teaching in Ambuhl is of cyclosporin and telmisartan is highly distinct from this compound both in structure and use. One of ordinary skill in the art would not reasonably consider that any teaching in Ambuhl related to cyclosporin would also apply to telmisartan merely because both compounds have some undefined water solubility problem. The fact that Ambuhl provides a very specific combination of components to achieve its objectives belies the conclusion that one of ordinary skill in the art would expect such specific combination to also be successfully used with any other active compound which has some undefined limit of water solubility – even compounds which are completely distinct in structure and use. The isolated teaching in Hauel for a completely different nature of composition is far too remote from the very specific compositions of Ambuhl to reasonably suggest their combination. To hold that they are combinable would mean that it would be obvious to combine any component from any active compound into a composition of a completely different active compound merely because the two actives share some general property in common. This is not supported by

the caselaw, particularly KSR.

For these three reasons alone, the rejections under 35 U.S.C. §103 should be withdrawn but the following additional comments are provided for completeness of the record.

Ambuhl teaches providing novel galenical compositions for a poorly water-soluble drug, such as a cyclosporin. The Ambuhl invention is particularly directed to the difficulties encountered with putting cyclosporins in a galenical composition. The difficulties addressed are not merely the poor solubility of the drug (see page 1, para. 0002) and Ambuhl does not specify what is means by "poorly water soluble." The Ambuhl compositions contain the cyclosporin, a solid polymer and/or a surfactant and a carrier; see para. 0008. The surfactant can be, among many other choices, a polyoxamer. The carrier can be, among other choices, a water-soluble carrier such as mannitol. The Ambuhl compositions are solid and in the form of a tablet, capsule or powder.

Ambuhl does not disclose any composition containing telmisartan or any teaching at all regarding telmisartan. Telmisartan and cyclosporin have no relation in structure or use. Further, Ambuhl provides no teaching or suggestion of using a basic agent, particularly NaOH, KOH, $NaHCO_3$, $KHCO_3$, Na_2CO_3, K_2CO_3, Na_2HPO_4, K_2HPO_4 or meglumine, in its compositions. To the contrary, Ambuhl is very specific and compreshensive about the possible components of its compositions. Ambuhl discusses many types of options for every possible component in its compositions. The fact that, despite this comprehensive discussion, it provides no hint to include a basic agent of the type recited in the claims would suggest to one of ordinary skill in the art that such an agent should be avoided. The specificity of its teachings belies the statement that its teachings would be reasonably expected to be applicable to any "poorly water soluble drug." One of ordinary skill in the art could only reasonably expect that Ambuhl's compositions could also be useful in other "poorly water soluble drugs" which have some structure and utility connection to cyclosporin.

Hauel discloses compounds of its generic formula (I) (page 1) which encompasses telmisartan. Telmisartan is specifically identified, e.g., in claim 6, as pointed out in the Office action. Hauel also provides a disclosure regarding compositions of its compounds generally, see page 53 and specific Examples I-VII at pages 113-118. In these specific examples, the composition is provided in the form of ampoules, tablets, capsules, oral suspensions and suppositories. The composition examples are not identified as being for any

specific active agent.

Hauel does not provide a general disclosure to include a basic agent component or a poloxamer component in its compositions. Examples IV and V contain lysine, which is a basic agent but is not NaOH, KOH, $NaHCO_3$, $KHCO_3$, Na_2CO_3, K_2CO_3, Na_2HPO_4, K_2HPO_4 or meglumine. Also Hauel discloses in Example II a composition which is a liquid composition in an ampoule which contains methyl glucamine (i.e., meglumine). Hauel does not disclose why the meglumine is added and provides no general discussion in the body of its disclosure which would indicate why meglumine would be added.

The additional rejection of claim 13 in view of Gaviraghi and Ohkouchi is traversed for the same reasons as above. The additional references are not cited for and do not remedy the deficiencies of the Ambuhl and Hauel references discussed above.

For all of the above reasons, applicants respectfully submit that the combined teachings of the cited references fail to render any of the instant claims obvious to one of ordinary skill in the art. Thus, the rejections under 35 U.S.C. §103 should be withdrawn.

The Third Rejection under 35 U.S.C. §103

The rejection of claim 13 under 35 U.S.C. §103, as being obvious over Applicants' admission of July 18, 2011 in view of Straub (US Pub. No. 2002/0019431), is respectfully traversed.

As noted in the Office action, the compositions subject to the prior sale (i.e., the admission of July 18, 2011) differ from the bilayer compositions of claim 13 in that the telmisartan-containing layer does not contain a poloxamer as recited in claim 13. However, this is not the only distinction. The prior sale compositions also differ in that they do not disclose a composition wherein the telmisartan-containing layer contains the basic agent and telmisartan in a "molar ratio of basic agent:telmisartan of 1:1 to 10:1."

As to the distinction on ratio, the prior sale compositions contain either 40 mg telmisartan and 12 mg meglumine or 80 mg telmisartan and 24 mg meglumine. Thus, the ratio is the same in both compositions. The molecular weight of telmisartan is 514.6 g/mol and the molecular weight of meglumine is 195.2 g/mol. For the 40 mg telmisartan and 12 mg meglumine composition, this calculates to .0777 mmol of telmisartan and .0614 mmol of meglumine, thus, a molar ratio of basic agent:telmisartan about 0.79:1, which is less than the minimum 1:1 of the claimed range. The other composition would have the same ratio.

There is no reason provided by or apparent from the prior sale items or those items in view of the Straub reference for modifying the molar ratio of basic agent:telmisartan. Absent any reason, there is no case for obviousness; see, e.g., KSR cited above. This distinction alone supports withdrawal of the rejection.

As to the distinction of poloxamer vs. povidone, the instant specification indicates that the presence specifically of component (b), the poloxamer of particular average molecular weight, is "essential to achieve a substantially improved dissolution of the active ingredient as well as for the use of a simplified manufacturing process." See, e.g., page 5, lines 23-26, of the instant specification. The art gives no indication of such an advantage for such poloxamers, specifically.

The mere prior sale compositions obviously give no suggestion or reason for one of ordinary skill in the art to modify the compositions to replace the povidone with a particular poloxamer as defined in the claims. Applicants also urge that Straub does not provide a motivation or reason for one of ordinary skill in the art to make such a substitution.

Straub is directed to a very specific composition of the drug celecoxib. Celecoxib is unrelated to telmisartan in chemical structure and use. In the Straub compositions, celecoxib is provided in a porous matrix composition. The porous compositions are made by combining the drug dissolved in a volatile solvent with a pore forming agent and removing the solvent and pore forming agent to provide a porous matrix of the drug. Straub optionally uses other excipients, one of which may be a wetting agent. See, e.g., page 2, paras. 0012-0013, of Straub. Such porous matrix compositions are very distinct in general nature and content from the prior sale compositions or claimed compostions. Straub discloses a number of wetting agents that could optionally be used in the compositions; see, e.g., page 3, paras. 0030-0032. Among such wetting agents are polyvinylpyrrolidone (povidone) and poloxamers, including Pluronic F68 (a.k.a. poloxamer 188).

Straub does not indicate that povidone and poloxamer 188 are equivalent for such use in Straub. Further, even if it did indicate equivalency for the use in Straub, such would not suggest equivalency or the ability to substitute in the prior sale compositions. The Straub compositions are completely distinct from the prior sale compositions in their use, preparation and active ingredient. One of ordinary skill in the art would have no rational basis to conclude from this teaching in Straub that one could substitute a poloxamer for povidone in the prior sale compositions. The agents are used for different purposes in very

different compositions and there is no connection between these compositions and the prior sale compositions. It is alleged in the Office action that such substitution would "yield a predictable result" but no rational basis for this allegation is provided. To the contrary, no reason can be seen for predicting the behavior of such wetting agents in the prior sale compositions based on their use for making porous compositions in Straub.

For each of the above reasons (and particularly for the combination of these reasons), it is urged that the prior sale compositions in view of Straub does not render the claimed invention obvious. Thus, the rejection under 35 U.S.C. §103 should be withdrawn.

It is submitted that the claims are in condition for allowance. However, the Examiner is kindly invited to contact the undersigned to discuss any unresolved matters.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,
/John A. Sopp/

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John A. Sopp, Reg. No. 33,103
Attorney/Agent for Applicant(s)

MILLEN, WHITE, ZELANO
& BRANIGAN, P.C.
Arlington Courthouse Plaza 1, Suite 1400
2200 Clarendon Boulevard
Arlington, Virginia 22201
Telephone: (703) 243-6333
Facsimile: (703) 243-6410

Attorney Docket No.: 01-1395
Date: December 1, 2011
JAS:dap